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**Remarks**

Claims 1-19, 21 and 23-40, inclusive, are under consideration.

The rejection of all remaining claims under 35 U.S.C. 103(a) as unpatentable over EP 0 461 662, or U.S. Patent No. 5,374,715 to Kanno, or U.S. Patent No. 4,532,089 to MacDonald, or WO 95/09610, individually or in combination, further in view of U.S. Patent No. 5,641,508 to Li et al. is not warranted, and is hereby traversed.

None of the primary references teach or suggest the claimed liposome constituents and the claimed proportions of constituents. In particular, EP 0 416 662 does not specify the fatty acids present in the claimed phospholipids, nor does this reference show or suggest the claimed proportions. Likewise, Kanno does not specify the fatty acids present in the claimed phospholipids, nor does it show or suggest the claimed proportions. The teachings of MacDonald and WO 95/09610 are similarly deficient and do not support the present rejection in whole or in part. Thus, regardless of whether these primary references are considered individually or collectively, the presently claimed liposomes and/or methods for their administration could not have been suggested to one of ordinary skill at the time the present invention was made.

Li et al., the secondary reference, does not cure the aforesaid shortcomings of the principal references. The ratios of DPPC to DOPE taught by Li et al. clearly do not suggest the claimed proportion of DPPC:DOPE:cholesterol of about 7:3:5. At column 12, line 12, Li et al. describe a preferred proportion of 5:2:3 for different constituents. This is a proportion that fails to suggest the claimed proportion to one of ordinary skill. The Examiner's own testimony that Li et al.'s preferred proportions of 5:2:3, as converted by the Examiner to 7:2.8:4.2, are "closer" to the claimed proportions also does not justify the rejection. They are and remain the same proportions as 5:2:3 whatever multiplier is applied to them. In addition, the 5:3:2 proportion is for different constituents than those presently claimed. See, for example, Li et al. at col. 12, lines 11-12. Also, there is no teaching in any of the primary references that would have led one of ordinary skill to select the liposomes of Li et al., not intended for systemic circulation (col. 32, lines 19-25), for systemic administration. As pointed out previously, the Li et al. liposomes of unspecified size deliver

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melanin and calcein to hair follicles after time periods measured in hours (col. 30, line 52, to col. 31, line 25). Thus, one of ordinary skill would not have had any motivation whatsoever to look to Li et al. when seeking to improve upon any of the teachings of the primary references.

The mere fact that the Examiner deems obvious to one of ordinary skill in the art to encapsulate any active material is of no moment and cannot support a rejection because that is not the statutory standard for obviousness under 35 U.S.C. 103(a).

The applied combinations of prior art references would not have suggested to one of ordinary skill in the relevant art the express limitations of the liposomes defined by claims 1-19 or the method of administration defined by independent claim 21 and dependent claims 23-40. By the Examiner's own admission, the primary references do not teach the administration of liposomes. What the Examiner deems obvious to one of ordinary skill is not the proper standard for patentability. Withdrawal of the foregoing obviousness rejection is requested.

The alternate rejection of all claims under 35 U.S.C. 103(a) based on the same principal references in view of Li et al. and Ostro (American Journal of Pharmacy) is traversed as well.

The shortcomings of the principal references in combination with Li et al. discussed above are equally applicable here. Ostro does not cure any of these deficiencies, but instead underscores the unobviousness of the present claims. The mere teaching that the half-life of relatively larger liposomes is in minutes would not have suggested to one of ordinary skill the specific limitations of the present claims. The attempted generalization from the teachings of Ostro et al. is not warranted in any event, and one of ordinary skill would not have done so.

In particular, the statement in Ostro et al. that the half-life of a liposomal preparation can be increased from minutes to hours refers to an earlier publication by Allen, *Biochimica et Biophysica Acta* 640:385-397 (1981) (copy enclosed for the Examiner's ready reference). The half times reported by Allen in Tables I & II at pages 388 and 389, respectively, show half-times that range from 1 hour  $\pm$  0.5 to 34.7 hours  $\pm$  7.9 hours. Thus, the shortest half-time reported by Allen is at least 30 minutes, a time period at least one order of magnitude greater than the claimed maximum residence time of 3 minutes. Moreover, the

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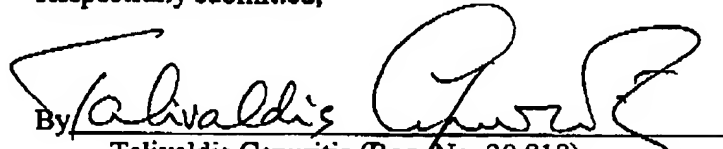
Allen data were obtained with liposome compositions vastly different from those presently claimed. Thus, even with addition of the Ostro et al. reference to the reference combination the present obviousness rejection is not sustainable.

Withdrawal of this rejection is earnestly urged.

Early passing of this application to issue is solicited.

Respectfully submitted,


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